

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 May 2001 (03.05.2001)

PCT

(10) International Publication Number
WO 01/30346 A1

(51) International Patent Classification⁷: A61K 31/4164,
31/155, 31/417, A61P 25/14, 25/16, A61K 31/00, 31/473,
48/00

(74) Agent: BANFORD, Paul, Clifford; Marks & Clerk,
Sussex House, 83-85 Mosley Street, Manchester M2 3LG
(GB).

(21) International Application Number: PCT/GB00/04046

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(22) International Filing Date: 20 October 2000 (20.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9924941.9 22 October 1999 (22.10.1999) GB

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): THE
VICTORIA UNIVERSITY OF MANCHESTER
[GB/GB]; Oxford Road, Manchester M13 9PL (GB).

(72) Inventors; and

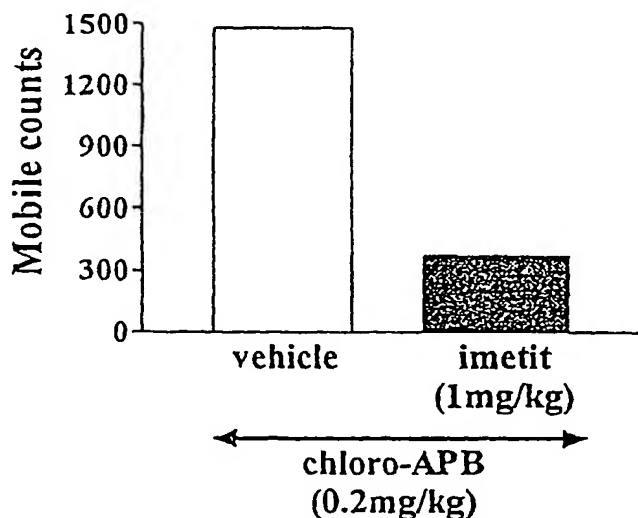
(75) Inventors/Applicants (*for US only*): BROTCHE,
Jonathan [GB/GB]; Flat 22, Regency House, 36 Whit-
worth Street, Manchester M1 3NR (GB). HILL, Michael
[GB/GB]; 87 Chestnut Street, Chadderton, Oldham OL9
8HF (GB). CROSSMAN, Alan [GB/GB]; School of Bio-
logical Sciences, Department of Neurosciences, Stopford
Building, University of Manchester M13 9PT (GB).

Published:

- With international search report.
- Before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments.

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: TREATMENT OF DYSKINESIA



(57) Abstract: The present invention relates to the use
of compounds that enhance H₃-histamine receptor ac-
tivity, or activation (e.g. H₃-histamine receptor agonists)
for the treatment of dyskinesia. The compounds are par-
ticularly useful for treating dyskinesia associated with
parkinsonian therapy.

WO 01/30346 A1

TREATMENT OF DYSKINESIA

The present invention relates to the treatment of dyskinesia.

Dyskinesias are characterised by the development in a subject of abnormal involuntary movements and may manifest as chorea (irregular, involuntary movements of the body, especially the face and extremities) or dystonia (disorder or lack of muscle tonicity).

One way in which dyskinesias may arise is as a side effect of dopamine replacement therapy for Parkinsonism or other basal ganglia-related movement disorders. Parkinsonism is a syndrome of symptoms characterised by slowness of movement (bradykinesia), rigidity and / or tremor. Parkinsonian symptoms are seen in a variety of conditions, most commonly in idiopathic parkinsonism (i.e. Parkinson's Disease) but also following treatment of schizophrenia, manganese poisoning, head injury and the like.

The use of dopamine-replacing agents (e.g. L-DOPA and apomorphine) as symptomatic treatments for conditions such as Parkinson's disease have undoubtedly been successful in increasing the quality of life of patients suffering from the conditions. However, dopamine-replacement therapy does have limitations, especially following long-term treatment. Problems can include a wearing-off of the anti-parkinsonian efficacy of the treatment and in particular the appearance of a range of side effects. These side effects may manifest as dyskinesias such as chorea and dystonia. Dyskinesia can be seen either when the patient is undergoing dopamine-replacement therapy (in the case of chorea and/or dystonia) or even when off therapy (when dystonia is prevalent). Ultimately, these side-effects severely limit the usefulness of dopaminergic treatments.

Many attempts have been made to develop agents that will prevent the development of, and/or treat, dyskinesias. For instance, attempts have been made to develop novel dopamine replacement therapies that will obviate or mitigate dyskinetic

side effects although such attempts have met with limited success. There is therefore a need to develop ways by which dyskinesias may be treated.

According to a first aspect of the present invention, there is provided a use of a compound which enhances H₃-histamine receptor activity, or activation, for the manufacture of a medicament for the treatment of dyskinesia.

According to a second aspect of the present invention, there is provided a composition for use in the treatment of dyskinesia comprising a therapeutically effective amount of a compound which enhances H₃-histamine receptor activity, or activation, and a pharmaceutically acceptable vehicle.

According to a third aspect of the present invention, there is provided a method for the treatment of dyskinesia comprising administering to a person or animal in need of such treatment a therapeutically effective amount of a compound which enhances H₃-histamine receptor activity, or activation.

H₃-histamine receptors are a subclass of histamine receptors which are found in neural tissues.

By "dyskinesia" we mean the development in a subject of abnormal involuntary movements. These movements may manifest as chorea (irregular, involuntary movements of the body, especially the face and extremities) or dystonia (disorder or lack of muscle tonicity). Such movements include ballistic movements and athetoid movements of the trunk, limbs and facial musculature.

The invention is based upon our studies relating to the neural mechanisms underlying movement disorders. Although we do not wish to be bound by any hypothesis, we believe that movement disorders involve abnormal activity of basal ganglia output pathways and in many cases this is brought about by abnormal function of striatal efferent pathways. These consist of a "direct" pathway to the medial or internal segment of the globus pallidus and the pars reticulata of the

substantia nigra and a "indirect" pathway to the lateral or external segment of the globus pallidus. One of the pathophysiological hallmarks of dyskinesia is overactivity of the direct striatal output pathway (In L-DOPA induced dyskinesia, this overactivity appears in part to be caused by an overstimulation of dopamine D₁-receptors). We believe compounds which enhance H₃-histamine receptor activity, or activation reduce the activity of the striatal output pathway and thereby reduce dyskinesia.

We have found that compounds which enhance H₃-histamine receptor activity, or activation are highly effective for the treatment of dyskinesias. For instance, we have found that dyskinesias (e.g. chorea and dystonia) do not develop, or are at least reduced, when the compounds are given to subjects on dopamine-replacement therapy for the treatment of a movement disorder.

Several classes of compound, which may be used according to the invention, are capable of enhancing H₃-histamine receptor activity. These compounds include:

- (i) H₃-histamine receptor agonists and partial agonists;
- (ii) compounds which enhance synthesis of endogenous H₃-histamine receptor agonists (e.g. histamine *per se*);
- (iii) compounds which enhance release of H₃-histamine receptor agonists;
- (v) compounds which block the rate of inactivation or metabolism of H₃-histamine receptor agonists (e.g. histamine-N-methyltransferase inhibitors such as 9-amino-1,2,3,4-tetrahydroacridine and SKF91488); and
- (vi) compounds which promote/increase H₃-histamine receptor expression and/or transcription.

The compound may modulate any type of histamine receptor provided that H₃-histamine receptor activity is enhanced (e.g. histamine *per se* may be used as an example of a H₃-histamine receptor agonist.). However it is preferred that the compound selectively enhances the activity of H₃-histamine receptors. By "selectively" we mean the compound enhances H₃-histamine receptor activity or activation to a greater extent than other types of histamine receptor (e.g. H₁- or H₂-receptors).

H₃-histamine receptor agonists ((i) above) are preferred compounds for use according to the invention. Selective H₃-histamine receptor agonists which are suitable for treating dyskinesias include Imetit, Imepip and R(-)-alpha-methylhistamine. One parameter by which selectivity of H₃ agonists may be assessed is by comparing binding affinities of a particular compound for each subclass of a receptor. Preferred selective H₃ agonists have a higher binding affinity for the H₃ receptor than for the H₁ and H₂ receptors.

The compounds (and compositions or medicaments containing them) may be used to treat many types of dyskinesia. For instance the compounds may be used to treat dyskinesia associated with Huntington's disease, idiopathic torsion dystonia, tardive dyskinesia or off-dystonia in Parkinson's disease and most particularly for dyskinesia associated with movement disorders such as parkinsonism (e.g. idiopathic Parkinson's disease, post-encephalitic parkinsonism or parkinsonism resulting from head injury), treatment of schizophrenia, drug intoxication, manganese poisoning and the like.

The compounds may also be used in the treatment of dyskinesias which manifest as hyperkinetic activity (e.g. Tourette's syndrome).

The compounds are also useful for treatment of dyskinesias which arise as a side-effect of other therapeutic agents. For instance, the compounds are useful for the treatment of dyskinesia associated with ropinirole, pramipexole, cabergoline, bromocriptine, lisuride, pergolide, L-DOPA or apomorphine treatment. The compounds are preferably used for the treatment of dyskinesia associated with L-DOPA or apomorphine treatment.

The compounds are particularly useful for treating dyskinesia caused by agents used to treat movement disorders such as parkinsonism. In this respect a preferred use of the compounds is in the treatment of dyskinetic side-effects associated with L-DOPA or apomorphine therapy for parkinsonism.

The compounds may be used to treat existing dyskinesias but may also be used when prophylactic treatment is considered medically necessary. For instance, when it is considered necessary to initiate L-DOPA therapy and it is feared that dyskinesias may develop.

The compounds may be used to treat dyskinesia as a monotherapy (i.e. use of the compound alone); as an adjunct to medicaments to prevent dyskinetic side-effects caused by the medicament (e.g. as an adjunct to L-DOPA or apomorphine given to treat parkinsonian patients) or alternatively the compounds may be given in combination with other compounds or treatments which also reduce dyskinesia (e.g. μ -opioid receptor antagonists, α_2 -adrenoreceptor-antagonists, cannabinoid CB₁-antagonists, NMDA receptor-antagonists, GPi lesion/deep brain stimulation).

The compositions of the first and second aspects of the invention may take a number of different forms depending, in particular on the manner in which the composition is to be used. Thus, for example, the composition may be in the form of a powder, tablet, capsule, liquid, ointment, cream, gel, hydrogel, aerosol, spray, micelle, liposome or any other suitable form that may be administered to a person or animal. It will be appreciated that the vehicle of the composition of the invention should be one which is well tolerated by the subject to whom it is given and enables delivery of the compounds to the brain.

The composition of the invention may be used in a number of ways. For instance, systemic administration may be required in which case the compound may be contained within a composition which may, for example, be ingested orally in the form of a tablet, capsule or liquid. Alternatively, the composition may be administered by injection into the blood stream. Injections may be intravenous (bolus or infusion) or subcutaneous (bolus or infusion). The compounds may also be administered by inhalation (e.g. intranasally).

Compounds enhancing H₃-histamine receptor activity may also be administered centrally by means of intracerebral, intracerebroventricular, or intrathecal delivery.

The compound may also be incorporated within a slow or delayed release device. Such devices may, for example, be inserted under the skin and the compound may be released over weeks or even months. Such a device may be particularly useful for patients with long term dyskinesia such as patients on continuous L-DOPA therapy for the treatment of Parkinsonism. The devices may be particularly advantageous when a compound is used which would normally require frequent administration (e.g. at least daily ingestion of a tablet or daily injection).

It will be appreciated that the amount of a compound required is determined by biological activity and bioavailability which in turn depends on the mode of administration, the physicochemical properties of the compound employed and whether the compound is being used as a monotherapy or in a combined therapy. The frequency of administration will also be influenced by the above mentioned factors and particularly the half-life of the compound within the subject being treated.

Known procedures, such as those conventionally employed by the pharmaceutical industry (e.g. *in vivo* experimentation, clinical trials etc), may be used to establish specific formulations of compositions and precise therapeutic regimes (such as daily doses of the compounds and the frequency of administration).

Generally, a daily dose of between 0.01µg/kg of body weight and 1.0g/kg of body weight of a compound which enhances H₃-histamine receptor activity may be used for the treatment of dyskinesia depending upon which specific compound is used more preferably the daily dose is between 0.01mg/kg of body weight and 100mg/kg of body weight.

Purely by way of example a suitable dose of imetit for treating L-DOPA or chloro-APB induced dyskinesia in subjects with Parkinson's disease is between

0.1mg/kg/day and 100mg/kg/day (depending upon the health status of the individual). It is preferred that between 0.25mg/kg/day and 20mg/kg/day of imetit is given to a person daily. For instance it is most preferred that about 1 – 5 mg/kg/day imetit is given for treating dyskinesia induced by 0.2mg/kg chloro-APB whereas about 5 - 20mg/kg/day imetit is particularly effective for treating dyskinesia induced by 8mg/kg L-DOPA.

It will be appreciated that the required dose will be effected by the route of administration. When imetit is given intravenously 0.1-10 mg/kg is a preferred dose whereas higher doses (e.g. 30 mg/kg) may be a suitable dose orally.

By way of further example suitable doses of 9-amino-1,2,3,4-tetrahydroacridine and SKF91488 are preferably 0.5-30 mg/kg.

Daily doses may be given as a single administration (e.g. a daily tablet for oral consumption or as a single daily injection). Alternatively the compound used may require administration twice or more times during a day. As an example, imepip for treating L-DOPA induced dyskinesia in patients with Parkinson's disease may be administered as two (or more depending upon the severity of the dyskinesia) daily doses of between 25mg and 5000mg in tablet form. A patient receiving treatment may take a first dose upon waking and then a second dose in the evening (if on a two dose regime) or at 3 or 4 hourly intervals thereafter. Alternatively a slow release device may be used to provide optimal doses to a patient without the need to administer repeated doses.

A preferred means of using protein or peptide compounds which enhance H₃-histamine receptor activity for the treatment of dyskinesias is to deliver the compound to the brain by means of gene therapy. For instance, gene therapy may be used to increase expression of H₃-histamine receptors, increase expression of enzyme(s) responsible for the synthesis of endogenous H₃-histamine receptor agonists (e.g. histamine *per se*), decrease expression of a protein which promotes breakdown or desensitisation of H₃-histamine receptors or decrease expression of a protein which

promotes breakdown of H₃-histamine receptor agonists. Therefore according to a fourth aspect of the present invention there is provided a delivery system for use in a gene therapy technique, said delivery system comprising a DNA molecule encoding for a protein which directly or indirectly enhances H₃-histamine receptor activity, said DNA molecule being capable of being transcribed to allow the expression of said protein and thereby treating a dyskinesia.

The delivery systems according to the fourth aspect of the invention are highly suitable for achieving sustained levels of a protein which directly or indirectly enhances H₃-histamine receptor activity over a longer period of time than is possible for most conventional therapeutic regimes. The delivery system may be used to induce continuous protein expression from cells in the brain that have been transformed with the DNA molecule. Therefore, even if the protein has a very short half-life as an agent *in vivo*, therapeutically effective amounts of the protein may be continuously expressed from the treated tissue.

Furthermore, the delivery system of the invention may be used to provide the DNA molecule (and thereby the protein which is an active therapeutic agent) without the need to use conventional pharmaceutical vehicles such as those required in tablets, capsules or liquids.

The delivery system of the present invention is such that the DNA molecule is capable of being expressed (when the delivery system is administered to a patient) to produce a protein which directly or indirectly has activity for enhancing H₃-histamine receptor activity. By "directly" we mean that the product of gene expression *per se* has the required activity. By "indirectly" we mean that the product of gene expression undergoes or mediates (e.g. as an enzyme) at least one further reaction to provide a compound effective for enhancing H₃-histamine receptor activity and thereby treating a dyskinesia.

The DNA molecule may be contained within a suitable vector to form a recombinant vector. The vector may for example be a plasmid, cosmid or phage. Such

recombinant vectors are highly useful in the delivery systems of the invention for transforming cells with the DNA molecule.

Recombinant vectors may also include other functional elements. For instance, recombinant vectors can be designed such that the vector will autonomously replicate in the cell. In this case, elements which induce DNA replication may be required in the recombinant vector. Alternatively the recombinant vector may be designed such that the vector and recombinant DNA molecule integrates into the genome of a cell. In this case DNA sequences which favour targeted integration (e.g. by homologous recombination) are desirable. Recombinant vectors may also have DNA coding for genes that may be used as selectable markers in the cloning process.

The recombinant vector may also further comprise a promoter or regulator to control expression of the gene as required.

The DNA molecule may (but not necessarily) be one which becomes incorporated in the DNA of cells of the subject being treated. Undifferentiated cells may be stably transformed leading to the production of genetically modified daughter cells (in which case regulation of expression in the subject may be required e.g. with specific transcription factors or gene activators). Alternatively, the delivery system may be designed to favour unstable or transient transformation of differentiated cells in the subject being treated. When this is the case, regulation of expression may be less important because expression of the DNA molecule will stop when the transformed cells die or stop expressing the protein (ideally when the dyskinesia has been treated or prevented).

The delivery system may provide the DNA molecule to the subject without it being incorporated in a vector. For instance, the DNA molecule may be incorporated within a liposome or virus particle. Alternatively the "naked" DNA molecule may be inserted into a subject's cells by a suitable means e.g. direct endocytotic uptake.

The DNA molecule may be transferred to the cells of a subject to be treated by transfection, infection, microinjection, cell fusion, protoplast fusion or ballistic bombardment. For example, transfer may be by ballistic transfection with coated gold particles, liposomes containing the DNA molecule, viral vectors (e.g. adenovirus) and means of providing direct DNA uptake (e.g. endocytosis) by application of the DNA molecule directly to the brain topically or by injection.

An embodiment of the present invention will now be described, by way of examples, with reference to the accompanying drawings, in which:

Figure 1 is a graph illustrating the effect of the H₃-histamine receptor agonist imetit on hyperkinesia following chloro-APB treatment of parkinsonian rats (a rodent behaviour that is mechanistically equivalent to dyskinesia in primates) in Example 1; and

Figure 2 is a graph illustrating the effect of the H₃-histamine receptor agonist imetit on L-DOPA-induced mobility (A) and dyskinesia (B) in MPTP-lesioned marmosets of Example 2 wherein ** $P < 0.01$ compared to L-DOPA + vehicle; non-parametric one-way repeated measures ANOVA (Friedman test) followed by Dunn's multiple comparison test.

EXAMPLE 1

The effect of the H₃-histamine receptor agonist imetit on dyskinesia was assessed in a reserpine-treated rat model of Parkinson's disease following treatment of the rats with the anti-parkinsonian agent chloro-APB (0.2mg/kg).

1.1. Methods**1.1.1 Treatments.**

Male Sprague-Dawley rats were split into two groups A and B. Rats in both groups were rendered parkinsonian by subcutaneous administration of reserpine (3mg/kg) for 18 hours.

After the 18 hours Group A were treated with chloro-APB (0.2 mg/kg) and imetit (1mg/kg) whereas B were treated with chloro-APB (0.2 mg/kg) and vehicle for imetit only.

1.1.2 Assessment of activity and mobility.

The locomotion of the rats in Groups A and B was measured over a one hour period using Benwick locomotor monitors. These locomotion monitors consist of a visually-shielded open-field arena, the perimeter of which is surrounded by a series of infra-red beams arranged at 5cm intervals. PC-based software (Amlogger) assesses the number of beams broken. The number of beams broken as part of a locomotor movement (mobile counts) or the number of beam breaks while the animal is not locomoting (static counts) were measured. In addition, the system assesses the time for which animals are mobile or static.

1.2 Results

Figure 1 illustrates that total mobile counts for imetit treated animals (A) was less than those treated with vehicle for imetit only (B). This demonstrates that there is a reduction in D₁-dopamine receptor-dependent locomotion (i.e. decreased activity via the direct striatal output pathway). In primates, dopamine D₁ receptor stimulation of the direct pathway is a key mechanism in generating dyskinesia and thus the reduction observed with imetit is indicative of a decrease in dyskinesia (see the description).

EXAMPLE 2

The effect of the H_3 -histamine receptor agonist imetit on L-DOPA-induced dyskinesia was assessed in the MPTP-lesioned marmoset model of Parkinson's disease.

2.1. Methods**2.1.1 Preparation of MPTP-lesioned marmoset model of Parkinson's disease**

Marmosets (*Callithrix jacchus*) (bred in a closed colony at the University of Manchester) are rendered parkinsonian by subcutaneous injection of 2mg kg^{-1} MPTP for 5 consecutive days. The marmosets are allowed to recover for a minimum of 10 weeks until their parkinsonism becomes stable. The degree of activity and disability before and after MPTP treatment is assessed using a combination of scales as described in section 2.1.2. Animals are then treated with L-DOPA for at least 3 weeks to prime them to elicit dyskinesia.

2.1.2 Assessment of behaviour

Behaviour was assessed using the following scales:

(a) Parkinsonian disability – non-parametric measures based on the following scales:

Mobility score: 0 = no movement, 1 = movement of head on the floor of the cage, 2 = movement of limbs, but no locomotion, on the floor of the cage, 3 = movement of head or trunk on wall of cage or perch, 4 = movement of limbs, but no locomotion, on wall of cage or perch, 5 = walking around floor of cage or eating from hopper on floor, 6 = hopping on floor of cage, 7 = climbing onto wall of cage or perch, 8 = climbing up and down the walls of the cage or along perch, 9 = running, jumping, climbing between cage walls / perch / roof, uses limbs through a wide range of motion and activity.

(b) **Dyskinesia** – non-parametric measures based on the following scale:

Dyskinesia score: 0 = Absent, 1 = Mild, fleeting, 2 = Moderate, not interfering with normal activity, 3 = Marked, at times interfering with normal activity, 4 = Severe, continuous, replacing normal activity.

The behavioural tests were assessed every 30 minutes for 4 hours, by *post hoc* analysis of video-recordings by an observer blinded to the treatment.

2.1.3 Treatments

Six marmosets received all treatments as described in table 1. The treatments were randomised such that on each day all six marmosets received one of the treatments. There was at least 48 hours washout between treatments.

Table 1

| Treatment number | Treatment | Route |
|------------------|------------------------------------|-------|
| 1 | L-DOPA (8mg/kg) + vehicle | oral |
| 2 | L-DOPA (8mg/kg) + imetit (1mg/kg) | oral |
| 3 | L-DOPA (8mg/kg) + imetit (3mg/kg) | oral |
| 4 | L-DOPA (8mg/kg) + imetit (10mg/kg) | oral |

2.2. Results

Figure 2 illustrates the effect of imetit treatment on L-DOPA-induced mobility (i) and dyskinesia (ii) in the MPTP-lesioned marmoset model of Parkinson's disease. These data demonstrate that imetit has no effect on L-DOPA-induced mobility. However, there is a dose-dependent reduction in the severity of L-DOPA-induced dyskinesia.

The MPTP-lesioned primate is the 'gold standard' preclinical model of Parkinson's disease. Therefore, these data are highly predictive of a beneficial therapeutic effect of H₃-histamine receptor agonists in the treatment of L-DOPA-induced dyskinesia in Parkinson's disease patients. Furthermore, these data suggest that the beneficial effect of imetit on L-DOPA-induced dyskinesia is not accompanied by a reduction in the therapeutic benefit of L-DOPA on mobility.

Although the data presented in these Examples demonstrate that H₃-histamine receptor agonists are useful for the treatment of dyskinesia associated with chloro-APB or L-DOPA therapy for Parkinson's disease, it will be appreciated that other compounds according to the present invention will be just as useful for treating other types of dyskinesias.

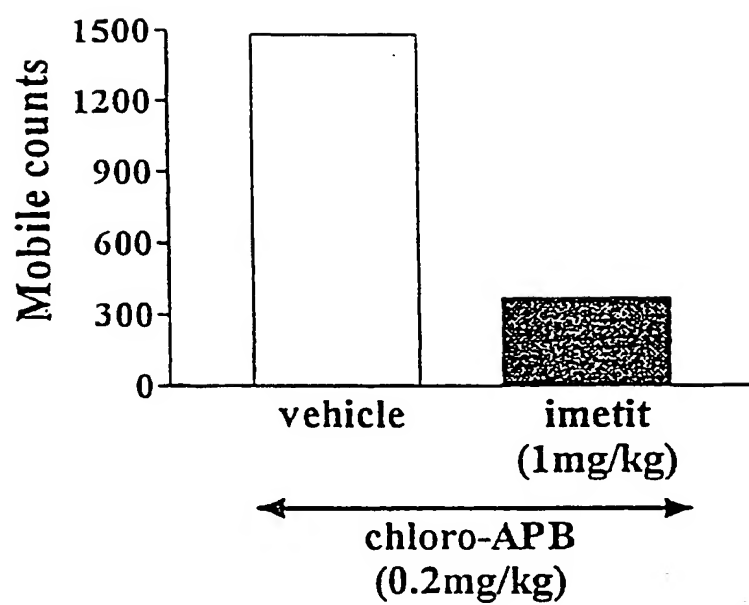
CLAIMS

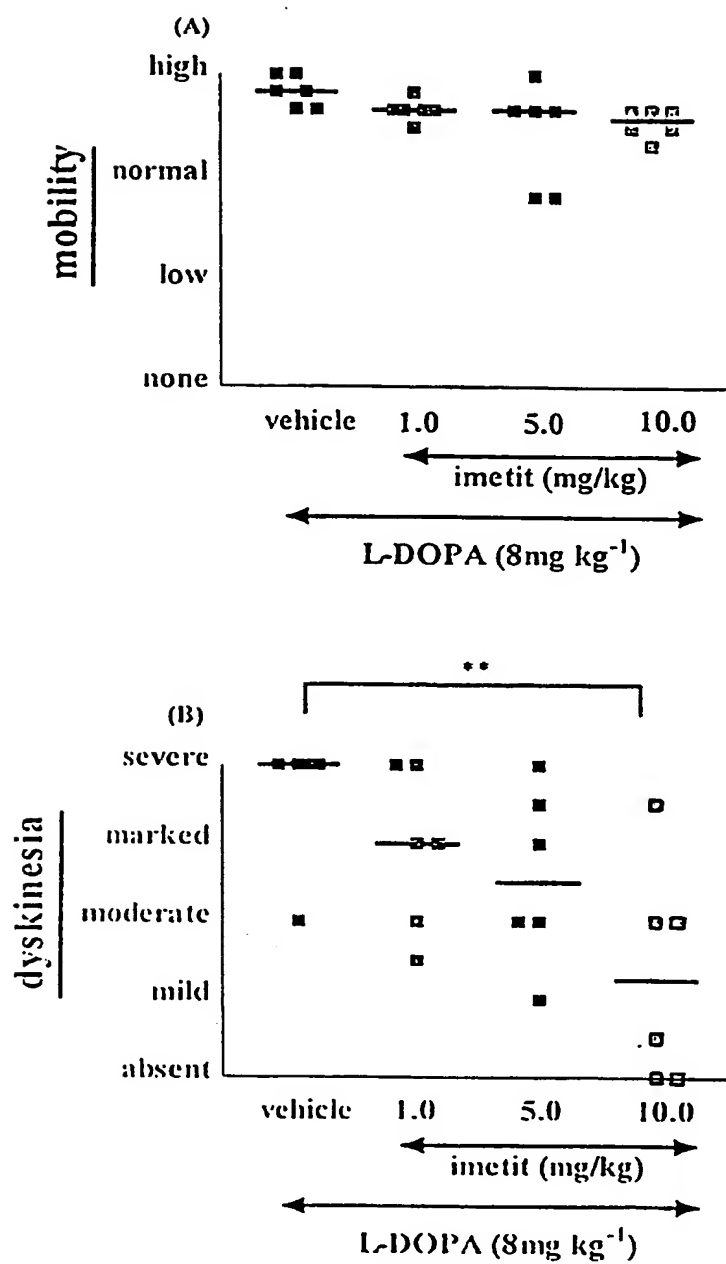
1. The use of a compound which enhances H₃-histamine receptor activity, or activation, for the manufacture of a medicament for the treatment of dyskinesia.
2. The use according to claim 1, wherein the compound is a H₃-histamine receptor agonist.
3. The use according to claim 2, wherein the compound is a selective H₃-histamine receptor agonist.
4. The use according to claim 3, wherein the agonist is selected from the group consisting of imetit, imepip and R(-)-alpha-methylhistamine.
5. The use according to claim 1 wherein the compound is an inhibitor of histamine-N-methyltransferase.
6. The use according to claim 5 wherein the compound is 9-amino-1,2,3,4-tetrahydroacridine or SKF91488.
7. The use according to any preceding claim, for the treatment of dyskinesia associated with movement disorders.
8. The use according to claim 7, for the treatment of dyskinesia associated with parkinsonism.
9. The use according to claim 8 wherein the parkinsonism is idiopathic Parkinson's disease or post-encephalitic parkinsonism.
10. The use according to claim 8 wherein the parkinsonism results from head injury, the treatment of schizophrenia, drug intoxication or manganese poisoning.

11. The use according to any one of claims 1 - 6 for the treatment of dyskinesia associated with Huntington's disease, idiopathic torsion dystonia, tardive dyskinesia or off-dystonia in Parkinson's disease.
12. The use according to any one of claims 1 - 6 for the treatment of dyskinesia which arises as a side-effect of a therapeutic agent.
13. The use according to claim 12 for the treatment of dyskinesia associated with agents used to treat movement disorders.
14. The use according to claim 12 or 13 wherein the agent is L-DOPA, Chloro-APB or apomorphine.
15. The use according to claim 12 wherein the agent is used to treat parkinsonism.
16. The use according to any preceding claim for prophylactic treatment of dyskinesia.
17. A composition for use in the treatment of dyskinesia comprising a therapeutically effective amount of a compound which enhances H₃-histamine receptor activity, or activation, and a pharmaceutically acceptable vehicle.
18. The composition according to claim 17 comprising a compound as defined in any one of claims 1 to 16.
19. A method for the treatment of dyskinesia comprising administering to a person or animal in need of such treatment a therapeutically effective amount of a compound which enhances H₃-histamine receptor activity, or activation.
20. The method according to claim 19 comprising administering a compound as defined in any one of claims 1 to 16.

21. A delivery system for use in a gene therapy technique, said delivery system comprising a DNA molecule encoding for a protein which directly or indirectly enhances H₃-histamine receptor activity, said DNA molecule being capable of being transcribed to allow the expression of said protein and thereby treat dyskinesia.

22. The use of a delivery system according to claim 21 for the manufacture of a medicament for the treatment of dyskinesia.

1/2FIG. 1

2 / 2FIG. 2

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/04046

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/4164 A61K31/155 A61K31/417 A61P25/14 A61P25/16
A61K31/00 A61K31/473 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, EMBASE, SCISEARCH, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|------------------------------------|
| X | <p>US 5 965 571 A (HUTCHINSON MICHAEL) 12 October 1999 (1999-10-12)</p> <p>abstract column 3, line 33 - line 58 column 6, line 4 -column 7, line 39 column 8, line 4 - line 5 column 8, line 63 - line 67 column 9, line 23 - line 36 column 11, line 4 - line 7 claims</p> <p style="text-align: center;">--- -/--</p> | <p>1,5-8, 13-15, 17-20</p> |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

27 March 2001

Date of mailing of the international search report

03/04/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Cielen, E

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/04046

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | <p>US 4 816 456 A (SUMMERS WILLIAM K) 28 March 1989 (1989-03-28) abstract column 3, line 60 -column 4, line 49 column 5, line 36 -column 6, line 36 column 9, line 59 - line 60 column 10, line 4 - line 42 column 11, line 23 - line 40 example 3 claims 1,4,6,13-15,24</p> | 1,5-8, 11,17-20 |
| X | <p>INGRAM N.A.W., NEWGREEN D.B.: "The use of Tacrine for tardive dyskinesia" AMERICAN JOURNAL OF PSYCHIATRY, vol. 140, no. 31, 1983, pages 16-29, XP000989784 the whole document</p> | 1,5-7, 11,17-20 |
| X | <p>J L JUNCOS ET AL: "CHOLINERGIC STRATEGIES IN TOURETTE SYNDROME: AN OPEN-LABEL TRIAL OF TACRINE HYDROCHLORIDE" NEUROLOGY,US,LIPPINCOTT WILLIAMS & WILKINS, PHILADELPHIA, vol. 48, no. 3, 1 March 1997 (1997-03-01), page A397 XP002087141 ISSN: 0028-3878 the whole document</p> | 1,5-7 |
| A | <p>CHIAVEGATTO, SILVANA ET AL: "Histamine and spontaneous motor activity: biphasic changes, receptors involved and participation of the striatal dopamine system" LIFE SCI. (1998), 62(20), 1875-1888 , XP000989725 abstract page 1876, paragraphs 2,4 page 1878, paragraph 3 figure 1 page 1880, paragraph 2 page 1882, paragraph 1 figure 5 page 1884, paragraph 1 page 1885, paragraph 3</p> | 1-4,7, 17-20 |

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/04046

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|--|-----------------------|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| A | SAKAI N ET AL: "EFFECTS OF THIOPERAMIDE, A HISTAMINE H3 RECEPTOR ANTAGONIST, ON LOCOMOTOR ACTIVITY AND BRAIN HISTAMINE CONTENT IN MAST CELL-DEFICIENT W/WV MICE" LIFE SCIENCES, GB, PERGAMON PRESS, OXFORD, vol. 48, no. 25, 1991, pages 2397-2404, XP002042695 ISSN: 0024-3205 abstract page 2398, paragraph 3 table 1 page 2402, paragraphs 2,3 | 1-4, 7, 17-20 |
| A | ITOH, YOSHINORI ET AL: "Neuronal histamine inhibits methamphetamine-induced locomotor hyperactivity in mice" NEUROSCI. LETT. (1984), 48(3), 305-9 , XP000989775 abstract page 305, paragraph 1 page 306, paragraph 5 figure 1 page 308, paragraph 4 | 1, 5, 7, 12, 16-20 |
| P, X | WO 00 20011 A (ORTHO MCNEIL PHARM INC) 13 April 2000 (2000-04-13) abstract page 1, line 25 -page 2, line 17 page 3, line 9 - line 12 page 8, line 1 - line 2 page 16, line 20 - line 26 page 18, line 11 - line 12 page 18, line 21 -page 19, line 11 page 19, line 23 - line 28 --- -/-- | 1-3, 17-22 |

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/04046

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------------|
| P,X | <p>HUOTARI M ET AL: "Effects of histamine H-3-ligands on the levodopa-induced turning behavior of hemiparkinsonian rats" PARKINSONISM & RELATED DISORDERS, (JUL 2000) VOL. 6, NO. 3, PP. 159-164. PUBLISHER: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND. ISSN: 1353-8020., XP000989734</p> <p>UNIV KUOPIO, DEPT PHARMACOL & TOXICOL, POB 1627, FIN-70211 KUOPIO, FINLAN (Reprint); UNIV KUOPIO, DEPT PHARMACOL & TOXICOL, FIN-70211 KUOPIO, FINLAND abstract</p> <p>page 159, column 1, paragraph 2 -column 2, paragraph 2</p> <p>page 160, column 2, paragraph 2</p> <p>page 160, column 2, paragraph 7 -page 161, column 1, paragraph 1</p> <p>figures 1A,B</p> <p>page 161, column 2, paragraph 1 -page 162, column 1, paragraph 2</p> <p>---</p> | 1-4,7,8, 12-20 |
| P,X | <p>HILL M P ET AL: "Histamine H3 receptors modulate dopamine D1 receptor-dependent locomotion in the reserpine-treated rat model of Parkinson's disease." SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 25, no. 1-2, 1999, page 171 XP000989999</p> <p>29th Annual Meeting of the Society for Neuroscience, Part 1; Miami Beach, Florida, USA; October 23-28, 1999</p> <p>ISSN: 0190-5295</p> <p>the whole document</p> <p>-----</p> | 1-4,7,8, 12-15, 17-20 |

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-3, 5, 7-22 relate to a compound which actually is not well-defined. The use of the definitions "a compound which enhances H3-histamine receptor activity, or activation", "a H3-histamine receptor agonist", "an inhibitor of histamine-N-methyltransferase", "a DNA molecule encoding for a protein which directly or indirectly enhances H3-histamine receptor activity, said DNA molecule being capable of being transcribed to allow the expression of said protein and thereby treat dyskinesia" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the compounds specifically mentioned in claims 4 and 6.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/04046

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|---|--|
| US 5965571 A | 12-10-1999 | AU 4078997 A WO 9807431 A | 06-03-1998 26-02-1998 |
| US 4816456 A | 28-03-1989 | AT 106245 T AU 671933 B AU 7888694 A AU 621035 B AU 8070787 A CA 1335813 A DE 3789967 D DE 3789967 T DK 295888 A EP 0328535 A EP 0595365 A FI 891548 A HK 1001669 A JP 6055725 B JP 2500975 T LU 88749 A MX 9203762 A WO 8802256 A | 15-06-1994 12-09-1996 09-02-1995 05-03-1992 21-04-1988 06-06-1995 07-07-1994 22-09-1994 07-06-1988 23-08-1989 04-05-1994 31-03-1989 03-07-1998 27-07-1994 05-04-1990 23-08-1996 01-09-1992 07-04-1988 |
| WO 0020011 A | 13-04-2000 | AU 1069299 A EP 1035856 A | 26-04-2000 20-09-2000 |